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**M E M O R A N D U M**

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**[Original signed by M Dong]**

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SUBJECT: COMMENTS ON THE PENTACHLOROPHENOL (PCP) TASK FORCE'S BIOMONITORING STUDY

Presented below are the comments on the PCP Task Force's recent study (Wilkinson, 1999) entitled "*Inhalation Dosimetry and Biomonitoring Assessment of Worker Exposure to Pentachlorophenol During Pressure-Treatment of Lumber*." In that study, daily exposures to PCP over three workdays were monitored for 22 workers applying the wood preservative to (utility) poles at five pressure-treatment facilities located in the United States and Canada. This review has its focus on the usefulness of the biomonitoring data only, since the daily doses calculated from the air samples were inconsequential when compared to those calculated from the urine samples (or from patch dosimetry data in other available studies).

1. The Task Force's biomonitoring study appeared to have followed an acceptably sound protocol in monitoring the worker exposure in question. Although to include more test subjects and more treatment facilities normally would give a greater statistical power and a better representation of the work tasks involved, such a problem with sample size is not unique to biomonitoring. The PCP residue levels in worker urine samples were determined by the analytical method Morse Method Meth-113 (Rev.2), which was found to have yielded acceptably high percent recoveries of PCP from the field-fortified urine samples.

2. The study report did not disclose explicitly the type of protective clothing that the workers wore on the three consecutive days during which their 24-hour urine samples were collected. It is assumed here that the statement "he/she would *normally* wear while working" means that the worker did not wear more than what the labels call for; otherwise, his or her daily exposure under label conditions would have been underestimated. This is highly unlikely the case, nonetheless, since workers are required by labels to wear such heavy protective clothing as overalls, jackets, *and* gloves.

3. The study report also did not detail the work history of the 22 workers. This piece of information is critical, despite the assurance by the Task Force that the worker's urinary residue level is likely to reach a "steady state" level by the middle of each work week. As pointed out by Braun *et al*. (1978) and further illustrated below in this review, theoretically a steady state level cannot be reached until the individual has been working in a treatment facility for 8 consecutive days (or likely longer for dermal exposure). This relatively long period is required for PCP to reach the steady state level because in the aforementioned

pharmacokinetics study by Braun *et al*., the human volunteers did not excrete all the 86% of the single oral dose in the urine until day 8.

4. In the biomonitoring study, the (total) daily exposures to PCP for the 22 workers were estimated from residue levels measured in their urine samples. The residue levels were adjusted both for the mean percent recovery (of PCP in field-fortified urine) and for the 86% excretion of absorbed PCP in urine (observed by Braun *et al*., 1978). These adjustments are deemed appropriate as well as necessary. However, as illustrated in Table 1 below, further adjustments on these residue levels are needed when acute exposure is considered.

5. Table 1 below summarizes the results of the simulation of repeated daily ingestion of 100 units of PCP by humans. The simulation results indicate that, as expected, PCP from repeated daily ingestion would reach a steady-state in 8 days. However, as further illustrated by the dotted area in the table, there are still approximately 203 units left (i.e., unaccounted for) in the body from previous ingestion. The simulation summarized in this table was based on the urinary excretion kinetics of PCP outlined in Figure 1 below. The urinary excretion outlined in Figure 1 is essentially the sum of the urinary excretion of PCP and the limited urinary excretion of PCP-G (the only measurable metabolite PCP glucuronide) presented in Figure 2 in Braun *et al*. (1978). Note that the excretion levels timed in Figure 1 and their corresponding levels in Table 1 differ by a factor of 2.22. This is because the excretions in Figure 1 were based on a 12-hour urine collection (as to be consistent with those presented in the 1978 paper by Braun *et al*.), whereas those in Table 1 were on a 24-hour collection plus an additional correction factor of 1.16 (= 100%/86%) to account for recovery of PCP from routes other than urine.

6. While Table 1 here shows a half-life of approximately 50 - 55 hours for elimination of PCP (including PCP-G), the urinary excretion curve (Figure 2) presented by Braun *et al*. (1978) appeared to reflect a half-life of about 15 to 20 hours longer than the one (33 hours) stated in their text. Previous studies suggested that PCP would reach a steady-state in about 7 days and 15 days, respectively, in rats (Braun *et al*., 1977) and in monkeys (Braun and Sauerhoff, 1976). There was also one additional metabolite (tetrachlorophydroquinone) found in the rat urine, whereas no metabolites were detected in the monkey excreta. These differences in the pharmacokinetic and metabolic fate of PCP among species are not totally unexpected, especially when the experimental doses given to the rats, the monkeys, and the human volunteers varied substantially. For instance, the oral doses of 10 and 100 mg of PCP/kg given to the rats are 100 to 1,000 times the dose ingested by the human volunteers. These greater doses given to the rats might just be sufficient to saturate the elimination process (hence resulting in a longer excretion half-life), or to increase the amount of cytochrome P-450 monooxygenases (or other biotransformation enzymes) in the rat liver to the level that (some of) the absorbed PCP could undergo another or an additional biotransformation process prior to its elimination. Although PCP was seen to reach a steady-state in about 7 or 8 days in both the human and the rat test subjects, one rat day is biologically equivalent to about 25 human days.

7. As discussed in Ross *et al*. (in press), percutaneous absorption and acquisition of most chemicals are slower than oral. Therefore, the time required for PCP to reach the steady-state in workers could be longer than the 8 days illustrated in Table 1.

8. **Thus based on the above considerations and observations, it is recommended that the absorbed doses calculated in the study report be further adjusted (increased) by a factor of 5 if acute exposure is considered**. The absorbed doses as presented should be increased five-fold for acute effects because PCP cannot reach a steady-state in an acute toxicity study (in which a single dose given only once is needed for the determination of an acute NOEL). As illustrated in Table 1, urine sample #2 (and #3) provides an estimate of 100 units of absorbed PCP when the total body burden of PCP on that day is actually 303 units. A correction factor of 5, instead of 3, is suggested here for the increase because, as mentioned earlier, the time required for PCP to reach the steady-state in workers could be longer than 8 days *and* because the excretion pattern might be different between doses absorbed dermally *vs*. orally. If the excretion pattern were, for example, 1%, 4%, 10%, 20%, 30%, 20%, 10%, 4%, and 1% in that order for 9 consecutive days, then there would be 400 units left unaccounted for, instead of 203 units as illustrated in Table 1. Urine sample #1 in Table 1 suggests that the absorbed doses calculated from the urine samples would be underestimated if the workers had a work history shorter than 4 or 5 days. However, the suggested correction factor of 5 is more than sufficient to offset this underestimation for acute exposure. For subchronic or chronic exposure, this underestimation would be offset by the difference between the *actual* (sub)chronic NOEL (that actually insured by the daily total body burden) and the delivered dose used as NOEL in a subchronic or chronic toxicity study.

References

Braun WH, Blau GE, Chenoweth MB (1978). The Metabolism/Pharmacokinetics of Pentachlorophenol in Man, and a Comparison with the Rat and Monkey. In: *Toxicology and Occupational Medicine* (Deichmann WE, Ed.). Elsevier/North Holland, New York, Amsterdam, Oxford, pp. 289-296.

Braun WH, Young JD, Blau GE, Gehring PJ (1977). The Pharmacokinetics and Metabolism of Pentachlorophenol in Rats. *Toxicol Appl Pharmacol* 41:395-406.

Braun WH, Sauerhoff MW (1976). The Pharmacokinetic Profile of Pentachlorophenol in Monkeys. *Toxicol Appl Pharmacol* 38:525-533.

Ross JH, Dong MH, Krieger RI (in press). Conservatism in Pesticide Exposure Assessment. *J Regul Toxicol Pharmacol.*

Wilkinson EJ (1999). Inhalation Dosimetry and Biomonitoring Assessment of Worker Exposure to Pentachlorophenol During Pressure-Treatment of Lumber. Study No. AA980307. Pentachlorophenol Task Force, Vulcan Chemicals, 1101 30th Street, NW, Suite 500, Washington DC 20007.

cc: Thomas Thongsinthusak

Table 1. Results of Simulation of Repeated Ingestion of 100 Units of PCP by Humans

| **Urinary Recovery of Daily Absorbed Dose (from Repeated Ingestion of 100 Units of PCP)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | (day 1) | (day 2) | (day 3) | (day 4) | (day 5) | (day 6) | (day 7) | (day 8) | (day 9) |
| | Dose 1 | Dose 2 | Dose 3 | Dose 4 | Dose 5 | Dose 6 | Dose 7 | Dose 8 | Dose 9 |
| sampling | | | | | | | | | |
| day 01 | 17.80 | | sample 1 | | | | | sample 2 | |
| day 02 | 26.66 | 17.80 | ↓ | | | | | ↓ | sample 3 |
| day 03 | 22.22 | 26.66 | 17.80 | | | | | | ↓ |
| day 04 | 15.55 | 22.22 | 26.66 | 17.80 | | | | ↓ | |
| day 05 | 8.78 | 15.55 | 22.22 | 26.66 | 17.80 | | | | ↓ |
| day 06 | 5.00 | 8.78 | 15.55 | 22.22 | 26.66 | 17.80 | | ↓ | |
| day 07 | 2.89 | 5.00 | 8.78 | 15.55 | 22.22 | 26.66 | 17.80 | | ↓ |
| day 08 | **1.10** | **2.89** | **5.00** | **8.78** | **15.55** | **22.22** | **26.66** | **17.80** | |
| day 09 | | 1.10 | 2.89 | 5.00 | 8.78 | 15.55 | 22.22 | 26.66 | 17.80 |
| day 10 | | | 1.10 | 2.89 | 5.00 | 8.78 | 15.55 | 22.22 | 26.66 |
| day 11 | | | | 1.10 | 2.89 | 5.00 | 8.78 | 15.55 | 22.22 |
| day 12 | | | | | 1.10 | 2.89 | 5.00 | 8.78 | 15.55 |
| | | | | | | 1.10 | 2.89 | 5.00 | 8.78 |
| | | total in this dotted box | | = | 202.91 | | 1.10 | 2.89 | 5.00 |
| | | | | | | | | 1.10 | 2.89 |
| | | | | | | | | | 1.10 |

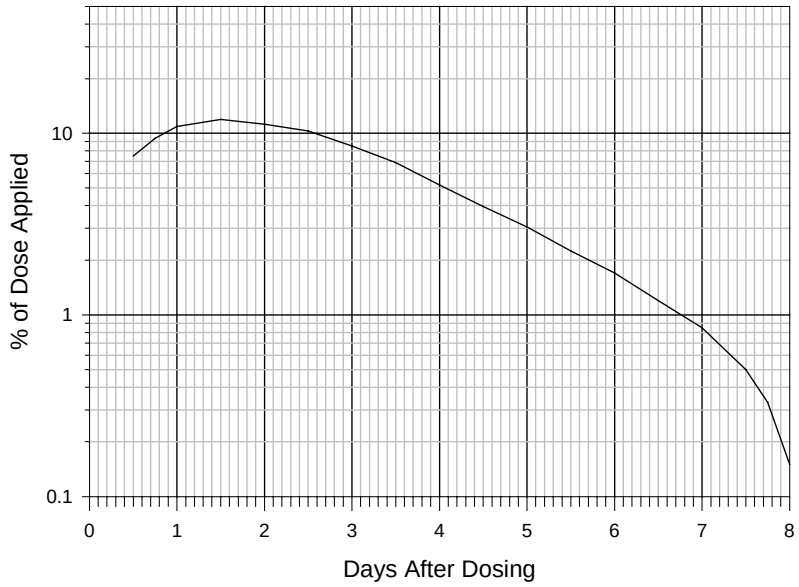


Figure 1. Average Urinary Excretion of PCP (and PCP-G) Following a Single Oral Dose to Human Volunteers